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Early-Life Phthalate Exposure and Adiposity at 8 Years of Age

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Background: Early-life phthalate exposure may influence child adiposity, but prior studies have not determined if there are periods of enhanced vulnerability to phthalates.

Objective: To examine the relationship between child adiposity at 8 y of age and repeated urinary biomarkers of phthalate exposure from gestation through childhood to determine if there are distinct periods of vulnerability.

Methods: In 219 mother–child pairs from Cincinnati, Ohio, we quantified nine urinary phthalate metabolites up to two times prenatally and six times from 1–8 y of age. We measured child body mass index (BMI), waist circumference, and percent body fat at 8 y of age. To identify periods of vulnerability, we used two statistical methods to estimate phthalate–adiposity associations at each visit, test differences in phthalate–adiposity associations across visits, and model trajectories of phthalate concentrations for children at different levels of adiposity.

Results: Prenatal phthalate concentrations were not associated with excess child adiposity. Monobenzyl phthalate (MBzP) concentrations during pregnancy and childhood were inversely associated with adiposity. The associations of di(2-ethylhexyl) phthalate ($\sum$DEHP) metabolites and monoethyl phthalate (MEP) with child adiposity depended on the timing of exposure. A 10-fold increase in $\sum$DEHP at 1 and 5 y was associated with a 2.7% decrease [95% confidence interval (CI): −4.8, −0.5] and 2.9% increase (95% CI: 0.3, 5.5) in body fat, respectively. MEP concentrations at 5 and 8 y of age were associated with higher child adiposity, but earlier childhood concentrations were not.

Conclusion: In this cohort, we did not find evidence of an obesogenic effect of prenatal phthalate exposure. Positive associations between postnatal MEP and $\sum$DEHP concentrations depended on the timing of exposure. https://doi.org/10.1289/EHP1022

Introduction

There is increasing recognition that the origins of obesity can be traced to gestation, infancy, or childhood, all critical periods of growth and development (Oken and Gillman 2003). Many studies have found associations between the fetal environment and subsequent health outcomes (Lawlor 2013; Ornoy 2011; Roseboom et al. 2006). The mechanisms that underlie the long-term health effects of the prenatal or early childhood environment are not fully understood, but likely include alterations in gene expression and hormonal systems to affect adipocyte differentiation, metabolism, and appetite (Heindel 2003; Stout et al. 2015). *In utero* or childhood exposure to some endocrine-disrupting chemicals (EDCs) may increase the risk of childhood obesity by affecting these mechanisms (Abbott et al. 2007; Romano et al. 2014; Tang-Péronard et al. 2011).

Phthalates are a class of EDCs that are widely used in some polyvinyl chloride plastics, personal care products, and food processing equipment. Exposure to phthalates is ubiquitous; studies have found that 100% of Americans are exposed to phthalates (Silva et al. 2004). Phthalates have well-documented antiandrogenic activity in rats and the potential to alter other hormonal pathways, like the hypothalamic–pituitary–adrenal axis and thyroid axis, which are important for growth and development (Boas et al. 2012; Howdeshell et al. 2008; Ma et al. 2011; Stout et al. 2015). Phthalates may also agonize or antagonize the peroxisome proliferation activated receptors, which are involved in a wide range of metabolic pathways, including cell differentiation, transcription, and metabolism (Casals-Casas et al. 2008).

Rodent and epidemiological studies suggest that phthalates may be chemical obesogens. Rodent studies show that prenatal exposure to di(2-ethylhexyl) phthalate (DEHP) causes obesity in mice and rats (Hao et al. 2012; Hao et al. 2013; Jia et al. 2016). While some epidemiological studies show that prenatal or childhood phthalate exposures are associated with child adiposity (Braun 2016), prior results are inconsistent, inferences about childhood exposures are limited by cross-sectional designs (Boas et al. 2010; Petrovicõová et al. 2016; Smerieri et al. 2015; Trasande et al. 2013), and most studies relied on a single measure of exposure during pregnancy or childhood (Botton et al. 2016; Buckley et al. 2016b; Deierlein et al. 2016; Teitelbaum et al. 2012; Valvi et al. 2015). In addition, few studies have comprehensively examined whether there are periods of heightened vulnerability to the potential obesogenic effects of phthalate exposures.

The purpose of this study was to examine the relationship between child adiposity at 8 y of age and repeated urinary biomarkers of phthalate exposure collected during gestation, infancy, and childhood to determine if there are distinct periods of vulnerability when the fetus or child is more vulnerable to the potential obesogenic effects of phthalate exposure.

Methods

Study Participants

We used data from the Health Outcomes and Measures of the Environment (HOME) Study, an ongoing prospective pregnancy and birth cohort study based in Cincinnati, Ohio. We recruited women into this study between 2003 and 2006. Eligibility

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requirements included that women were ≥18 years of age, less than 19 wk of gestation, and living in the Cincinnati, Ohio, area in a home built before 1978. Additional details regarding participant eligibility, recruitment, study design, and follow-up are described elsewhere (Braun et al. 2017). The HOME Study enrolled 389 women that gave birth to live singleton infants; the present analyses included 219 singleton infants who had at least one prenatal and one postnatal phthalate biomarker measure, anthropometric data at 8 y of age, and covariate information. All women provided informed consent for themselves and their children, and the institutional review boards (IRBs) at Cincinnati Children's Hospital Medical Center and the Centers for Disease Control and Prevention (CDC) approved this study. Brown University relinquished IRB authority to Cincinnati Children's Hospital Medical Center with an Interagency Agreement.

Phthalate Exposure Assessment

We collected maternal urine samples in polypropylene specimen cups twice during pregnancy, at approximately 16- and 26-wk gestation. We collected child urine samples annually from 1–5 y of age and again at 8 y of age. Urine was collected into surgical inserts placed into a diaper for children who were not toilet-trained, into a training toilet lined with inserts for children who were being toilet-trained, or into polypropylene specimen cups for children who were toilet-trained. All urine samples were refrigerated until processing and stored at or below –20 °C until chemical analysis.

We quantified urine concentrations of monoethyl phthalate (MEP), mono-*n*-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), mono(3-carboxypropyl) phthalate (MCPP), monobenzyl phthalate (MBzP), and four metabolites of DEHP: mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP) with analytic chemistry methods (Silva et al. 2004). The limits of detection ranged from 0.1 to 1.0 ng/mL (Silva et al. 2004). To account for urine dilution, phthalate metabolite concentrations were creatinine-standardized by dividing phthalate metabolite concentrations (ng/mL) by creatinine concentrations (mg/dL) and multiplying by 100. These creatinine-standardized values were then $\log_{10}$-transformed. If a woman provided more than one urine sample during pregnancy, as was the case for 208 women (95%), we averaged two $\log_{10}$- transformed phthalate concentrations from the two measures.

We were not able to quantify concentrations of MEHP, MnBP, and MiBP at 1–3 y of age because we detected these metabolites in the diaper inserts (Watkins et al. 2014). Thus, to create a consistent DEHP measure across the maternal and child samples, we only used the three oxidative DEHP metabolites (MEOHP, MEHHP, and MECPP) to create $\sum$DEHP by dividing each metabolite by its molar mass and summing the concentrations.

Child Adiposity

We assessed child adiposity at 8 y of age using body mass index (BMI), waist circumference, and percent total body fat. Trained research assistants who were blinded to mother and children's urinary phthalate metabolite concentrations conducted all anthropometry measurements in triplicate using standardized methods. Height and weight measurements were used to construct age- and sex-standardized BMI *z*-scores using CDC reference data from U.S. children (Kuczmarski et al. 2000). We estimated percent body fat using data provided by a Tanita bioelectric impedance scale.

Covariates

We used a directed acyclic graph to select covariates and considered maternal sociodemographic, perinatal, nutritional, environmental, and child factors (Figure S5) (Greenland et al. 1999; Textor et al. 2011). Maternal sociodemographic factors, including maternal age, race, income, marital status, and insurance status, were assessed using standardized interviews administered by trained research assistants during pregnancy. Maternal nutritional factors, including food security, prenatal vitamin use, and frequency of fruit/vegetable and fish consumption during the second or third trimester of pregnancy were assessed using standardized interviews. Serum cotinine, a sensitive and specific marker of active and secondhand tobacco smoke exposure, was measured using previously described methods (Bernert et al. 1997; Braun et al. 2010). Perinatal factors, including parity and maternal midpregnancy BMI (calculated from height and weight measurements taken at approximately 16-wk gestation), were abstracted from medical records. Depressive symptoms at 20-wk gestation were assessed using the Beck Depression Inventory-II® (Beck et al. 1996). Maternal breastfeeding duration was assessed with a standardized questionnaire. Child diet and physical activity at 8 y of age were assessed via parent-reported frequency of fast food, fish, and vegetable consumption and number of hours per day spent playing outdoors and watching television, respectively.

Our final adjusted models included maternal age at delivery, race, marital status, insurance, income, education, parity, cotinine, depressive symptoms, midpregnancy BMI, food security, fruit/vegetable and fish consumption during pregnancy, prenatal vitamin use, child sex, and child age at the 8-y visit. Models using BMI *z*-scores did not include child sex or age at the 8-y visit, as the *z*-scores were already age- and sex-standardized.

Statistical Analyses

We began our analyses by describing the central tendency and distribution of child adiposity at 8 y of age according to covariates. Because phthalate concentrations could be correlated over time due to shared exposure sources, we calculated the Pearson correlation coefficients between the average of the two prenatal phthalate measurements and the six postnatal measurements to determine if prenatal or postnatal exposure should be considered a confounder when estimating the effect of postnatal or prenatal phthalate exposure, respectively (Engel and Wolff 2013). We used scatterplots and LOESS smooth curves to examine the relationships between outcome and predictors.

To determine if there are periods of vulnerability to phthalate exposure, we used a multiple informant method using linear regression where each of the different exposure periods (average prenatal, 1 y, 2 y, 3 y, 4 y, 5 y, 8 y) are treated as informants (Sánchez et al. 2011). We used this method to jointly estimate the difference in adiposity for a 10-fold increase in each phthalate metabolite in every period. It is important to note that each exposure period is adjusted for the same covariates, but does not adjust for phthalate concentrations at other periods. This method also provides a 6-degree-of-freedom heterogeneity test statistic that tests whether the timing of exposure modifies the exposure–outcome associations. Lower heterogeneity *p*-values provide more evidence that at least one of the exposure–outcome associations differs from the rest, whereas higher *p*-values provide less evidence that the timing of exposure modifies the exposure–outcome association. Separate analyses were conducted for each phthalate metabolite.

We created a summary variable of postnatal phthalate exposure by averaging children's urinary phthalate metabolite concentrations from visits at 1–5 and 8 y of age. We then estimated the

difference in adiposity at 8 y of age with a 10-fold increase in prenatal and average postnatal phthalate metabolite concentrations while adjusting for both periods of exposure.

Sensitivity Analyses

First, we examined whether child sex modified the association between urinary phthalate metabolite concentrations and child adiposity by including all two- and three-way product interaction terms between urinary phthalate metabolite concentrations, child sex, and visit. We examined the magnitude and precision of associations within strata, as well as the three-way product interaction term p-value that indicates if the pattern of associations between repeated phthalate concentrations and child adiposity differs by sex. We also conducted analyses adjusting for creatinine as opposed to standardizing by creatinine. Next, we conducted analyses adjusting for maternal weekly weight gain, infant birth weight, duration of breastfeeding, and child diet and physical activity at 8 y of age. To account for temporal trends in phthalate biomarkers, we included a term for year of the 16-wk prenatal urine sample collection. Next, we excluded women ($n=30$) with one or more of the following medical conditions that may impact fetal growth and prenatal phthalate metabolism and excretion: gestational diabetes, pregnancy-induced hypertension, preeclampsia, chorioamnionitis, placenta previa, or placental abruption. We also conducted analyses after excluding children that were born preterm ($n=18$). Finally, because of the correlation between prenatal and postnatal concentrations of some urinary phthalate metabolites, we included prenatal concentrations of some phthalate metabolites in models with postnatal concentrations of those same phthalate metabolites and vice versa.

To ensure that our postnatal results examining periods of vulnerability were robust to model assumptions, we also used a two-stage model to estimate the longitudinal pattern of child urinary phthalate metabolite concentrations for different levels of child adiposity at 8 y of age (Sánchez et al. 2011). The model provides a covariate-adjusted estimate of the pattern of urinary phthalate metabolite concentrations over childhood for different levels of child adiposity. We compared longitudinal patterns of childhood urinary phthalate metabolite concentration at the 25th, 50th, and 90th percentiles of covariate-adjusted BMI z-scores, waist circumference, and body fat percentage at 8 y of age. We also estimated the percent difference in urinary phthalate metabolite concentrations over time among children at the 90th percentile of child adiposity compared to children at the 50th percentile at 8 y of age. Additional details regarding this modeling technique are described in Supplemental Material.

Results

Women in our study were predominantly White (60%), married (62%), and had a household income >$40,000 per year (57%) (Table 1). Characteristics of those who completed follow-up at 8 y of age were similar to those who initially enrolled in the study and had live births (Braun et al. 2017). Further, prenatal phthalate concentrations did not differ between children who did and did not complete follow-up at 8 y of age (Table S1). Women who were included in these analyses had slightly lower household income, were more likely to be non-Hispanic black, were less likely to have private insurance, and were more likely to have a male infant than those who were not (Table S2).

Of the 219 children in our sample, 42% ($n=91$) had all 6 postnatal phthalate measures, 24% ($n=52$) had 5 postnatal measures, 14% ($n=31$) had 4 postnatal measures, 11% ($n=25$) had 3 postnatal measures, 5% ($n=10$) had 2 postnatal measures, and 5% ($n=10$) had 1 postnatal measure. The number of children included at each time point in the multiple informant model ranged from 138 to 219 (Tables S3–S5). There was a minimum of a 100-fold variation in each phthalate metabolite concentration, allowing us to analyze phthalate concentrations on a $\log_{10}$ scale (Table S8). We observed weak to moderate correlations between urinary MEP and MBzP concentrations in mothers during pregnancy and their children at 1–8 y of age (Pearson $r=0.19-0.39$) (Table 2). Prenatal and postnatal concentrations

Table 1. Body fat percentage at 8 y of age by covariates among Health Outcomes and Measures of the Environment (HOME) Study children.

Characteristic	n (%)	Mean body fat percentage (SD)
Overall	219	21.0 (6.5)
Maternal age (years)		
<25	58 (26)	22.2 (7.9)
25–35	130 (59)	20.7 (5.8)
>35	31 (14)	20.5 (6.8)
Household income ($/year)		
<20,000	58 (27)	22.9 (8.1)
20–<40,000	34 (16)	21.3 (6.8)
40–<80,000	71 (32)	20.1 (5.6)
≥80,000	56 (25)	20.0 (5.1)
Race		
Non-Hispanic white	132 (60)	19.7 (5.4)
Black	76 (35)	23.2 (7.6)
Other	11 (5)	21.9 (7.9)
Marital status		
Married	135 (62)	20.1 (5.8)
Unmarried, cohabiting	26 (12)	21.4 (6.4)
Unmarried, living alone	58 (26)	23.1 (7.7)
Education		
<High school	24 (11)	23.6 (7.4)
High school or some college	101 (46)	20.4 (5.9)
Bachelors or more	94 (43)	21.1 (6.9)
Serum cotinine concentrations		
<0.015 ng/mL (Unexposed)	69 (31)	19.6 (5.0)
0.015–3 ng/mL (Secondhand)	123 (56)	21.7 (7.1)
>3 ng/mL (active smoker)	27 (12)	21.9 (7.1)
Depressive symptoms		
Minimal	171 (78)	20.5 (6.4)
Mild	29 (13)	21.9 (6.3)
Moderate/severe	19 (9)	25.1 (7.3)
Parity at enrollment		
Nulliparous	100 (45)	20.8 (6.0)
1	65 (30)	20.7 (7.1)
≥2	54 (25)	21.9 (6.9)
Insurance		
Private	152 (69)	20.4 (6.0)
Public/uninsured	67 (31)	22.5 (7.5)
Food security		
Enough	162 (74)	20.8 (6.3)
Not kinds of food wanted or not enough	57 (26)	21.9 (7.2)
Maternal fish consumption		
Weekly	49 (22)	21.3 (6.6)
Monthly	77 (35)	20.7 (6.7)
Infrequent	93 (43)	21.2 (6.5)
Maternal fruit/vegetable consumption		
Daily	76 (35)	21.7 (7.2)
Weekly	116 (52)	20.5 (5.8)
Monthly	27 (12)	21.5 (7.8)
Child sex		
Female	122 (56)	22.9 (7.2)
Male	97 (44)	18.7 (4.8)
Maternal body mass index (kg/m^2) at 16-wk gestation		
Underweight–normal (≤24.99)	89 (41)	19.1 (5.4)
Overweight (25–29.9)	74 (33)	20.9 (5.4)
Obese (≥30)	57 (26)	24.2 (8.3)
Prenatal vitamin use		
None	33 (15)	22.0 (7.6)
Any	186 (85)	20.8 (6.4)

Note: SD, standard deviation.

Table 2. Correlation between average prenatal urinary phthalate metabolite concentrations and child urinary phthalate metabolite concentrations at 1, 2, 3, 4, 5, and 8 y of age in the Health Outcomes and Measures of the Environment (HOME) study.

Phthalate metabolite	Age in years (n)					
	1 y (184)	2 y (165)	3 y (169)	4 y (141)	5 y (170)	8 y (219)
$\sum$DEHP	0.12	0.17*	0.13	0.23*	0.02	0.17*
MCPP	0.03	0.22*	0.22*	0.38*	0.05	0.03
MnBP	-	-	-	0.36*	0.09	0.03
MiBP	-	-	-	0.32*	0.14	−0.02
MEP	0.20*	0.35*	0.35*	0.39*	0.29*	0.26*
MBzP	0.19*	0.27*	0.30*	0.32*	0.26*	0.23*

Note: Pearson correlation between $\log_2$-transformed, non–creatinine-standardized, average prenatal phthalate metabolite concentrations and $\log_2$-transformed concentrations at ages 1–5 and 8 years of age. Di(2-ethylhexyl) phthalate ($\sum$DEHP) metabolites is the sum of mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP). We did not quantify urine concentrations of MEHP, MnBP, and MiBP at 1–3 y of age because we detected the parent compounds of these metabolites in the diaper inserts. MBzP, monobenzylphthalate; MCPP, mono(3-carboxypropyl)phthalate; MEP, monoethylphthalate; MiBP, mono-isobutyl phthalate; MnBP, mono-n-butyl phthalate. *$p < 0.05$.

of other phthalate metabolites were not consistently correlated with each other (Table 2).

We collected anthropometric data at an average (±standard deviation) age of 8.1 (±0.6) y of age. The three child adiposity measures at 8 y of age were highly correlated with each other (Pearson $r = 0.80 - 0.85$).

Results from the multiple informant models suggested that associations of urinary $\sum$DEHP and MEP concentrations with child adiposity at 8 y of age depended on the timing of exposure (Figure 1, Tables S3–S5); p-values for the interaction of DEHP and visit ranged from 0.06 to 0.37, and p-values for the interaction of MEP and visit ranged from 0.02 to 0.07, depending on outcome. While prenatal and 8-y $\sum$DEHP concentrations had no association with adiposity at age 8, associations between concentrations at 1 and 2 y of age and adiposity were inverse in direction, while associations at 3, 4, and 5 y were positive in direction (Figure 1). For example, a 10-fold increase in urinary $\sum$DEHP concentrations at 1 y of age was associated with a 2.7% decrease [95% confidence interval (CI): −4.8, −0.5] in body fat at age 8, while a 10-fold increase at 5 y was associated with a 2.9% increase (95% CI: 0.3, 5.5) (Figure 1, Table S3). The association between urinary MEP concentrations and child body fat percent became increasingly positive in direction with increasing child age; going from being null during pregnancy ($\beta = -0.3$, 95% CI: −1.9, 1.2) and 1–4 y of age, to positive at 8 y of age ($\beta = 1.8$, 95% CI: 0.0, 3.6) (Figure 1, Table S3).

The associations of MnBP, MiBP, MBzP, and MCPP concentrations with child adiposity at age 8 did not depend on the timing of exposure (all p-values for the interaction terms of phthalate and visit were >0.19). While associations between urinary MnBP, MiBP, and MCPP concentrations and child adiposity were predominantly null, urinary MBzP concentrations at most periods were associated with reduced adiposity, with the strongest associations observed with prenatal exposure; a 10-fold increase in prenatal urinary MBzP concentrations was associated with a 1.7% reduction in body fat at age 8 (95% CI: −3.6, −0.2).

When we examined average postnatal phthalate metabolite concentrations, our results were more precise compared to analyses using concentrations from each age (Table S7). Each 10-fold

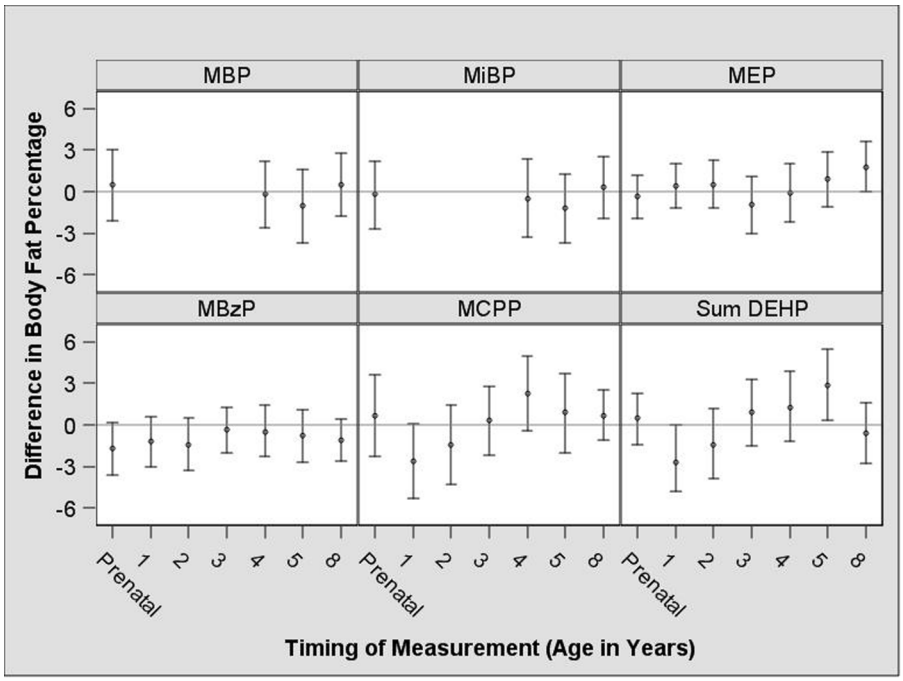

Figure 1. Adjusted difference in child body fat percentage at 8 y of age per 10-fold increase in urinary phthalate metabolite concentrations during pregnancy and at 1, 2, 3, 4, 5, and 8 y of age in the Health Outcomes and Measures of the Environment (HOME) Study. Adjusted for maternal age at delivery, race, marital status, insurance, income, education, parity, cotinine, depressive symptoms, midpregnancy body mass index (BMI), food security, prenatal fruit/vegetable and fish consumption, prenatal vitamin use, child sex, and child age at the 8-y visit. Monoethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), mono(3-carboxypropyl) phthalate (MCPP), monobenzyl phthalate (MBzP). Di(2-ethylhexyl) phthalate ($\sum$DEHP) metabolites is the sum of mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP). We did not quantify urine concentrations of MnBP and MiBP at 1–3 years of age because we detected the parent compounds of these metabolites in the diaper inserts. Interaction p-value indicating whether the timing of exposure modifies the association between phthalate concentrations and body fat was MnBP ($p = 0.78$), MiBP ($p = 0.77$), MEP ($p = 0.07$), MBzP ($p = 0.83$), MCPP ($p = 0.19$), and $\sum$DEHP ($p = 0.09$). Results for BMI z-score and waist circumference were similar, as the outcomes were highly correlated with each other (Pearson $r \geq 0.8$).

increase in average postnatal urinary MBzP concentration was associated with a 1.9% reduction in body fat at age 8 (95% CI: −2.9, −0.8), while each 10-fold increase in average postnatal urinary MEP concentration was associated with a 2.3% increase in body fat at age 8 (95% CI: 1.3, 3.3).

The pattern of association between repeated urinary phthalate metabolite concentrations and child BMI z-score, waist circumference, and body fat percent were similar (Tables S4 and S5).

With one exception, we found little evidence that the pattern of association between repeated urinary phthalate metabolite concentrations and child adiposity at 8 y of age was modified by child sex (p-values for 3-way interaction terms for sex, visit, and phthalate were all ≥0.64). However, child sex modified the pattern of associations between repeated urinary $\sum$DEHP concentrations and adiposity (p-values for 3-way interaction terms for sex, visit, and phthalate ranged from 0.05 to 0.30), where the pattern of associations in girls was similar to the associations among all children, and the pattern of associations was null in boys (Figure S1).

Our MBzP, MEP, and $\sum$DEHP results were not substantially different when we adjusted for creatinine, adjusted and standardized, or when we did not account for creatinine, as opposed to only standardizing, although associations between urinary MEP concentrations at age 8 and adiposity at age 8 were slightly attenuated when only adjusting. Associations of child adiposity with prenatal MEP, prenatal MBzP, and 8-y MEP were also attenuated towards the null when we did not account for creatinine compared to any other method of accounting for urine dilution.

Further, we did not see substantial differences in results when we excluded women with medical conditions and infants who were born preterm, or when we adjusted for maternal weekly weight gain, infant birth weight, breastfeeding duration, or year of urine collection. When adjusting for child diet and physical activity at 8 y of age, associations between prenatal urinary phthalate metabolite concentrations and body fat percentage were more strongly inverse for MEP (β: −1.1, 95% CI: −2.9, 0.7) and MBzP (β: −2.5, 95% CI: −4.7, −0.2), and more strongly positive for $\sum$DEHP (β: 1.4, 95% −0.7, 3.5). However, associations between 8-y urinary MEP concentrations and body fat percentage were attenuated towards the null (β: 1.1, 95% CI: −1.1, 1.3) (Table S6). Furthermore, we did not observe a substantial change in the results when prenatal phthalate concentrations were included as covariates for postnatal measures or when postnatal concentrations were included as covariates for prenatal measures (Table S6).

For our trajectory models, we focused on MBzP, MEP, and $\sum$DEHP because the multiple informant models showed that MBzP concentrations in each period were consistently inversely associated with adiposity, and that the associations of childhood MEP and $\sum$DEHP concentrations with adiposity depended on the timing of exposure. Compared to children who had lower percentiles of body fat at age 8, children at the 90th percentile of body fat tended to have lower MBzP concentrations at 1–4 and 8 y of age (Figure 2, Figure S2); higher MEP concentrations at all time points, but particularly at ages 5 and 8 y (Figure 3, Figure S3); and lower $\sum$DEHP concentrations at 1–2 y of age and higher $\sum$DEHP concentrations at 4–5 y of age (Figure 4, Figure S4). For example, children in the 90th percentile of body fat percentage at 8 y of age had geometric mean urinary MBzP concentrations of 10.8 ng/mL at 1 y of age, while children in the 50th and 25th percentiles of body fat percentage had average MBzP concentrations of 12.5 ng/mL and 13.1 ng/mL at 1 y, respectively.

Discussion

To the best of our knowledge, this is the first study to use repeated phthalate measurements during gestation, infancy, and childhood and determine whether the fetus, infant, or child is more vulnerable to the potential obesogenic effects of phthalate exposure during distinct periods of development. Using eight repeated urinary phthalate biomarkers between the second trimester of pregnancy and 8 y of age, we found evidence that the association between some urinary phthalate metabolite concentrations and child adiposity depended on the timing of exposure. The results from the two models we used to assess periods of vulnerability to phthalates provided similar observations, suggesting that our results were robust to assumptions made by each of the models.

We are aware of seven prospective epidemiological studies that examined prenatal phthalate exposure and childhood adiposity. One study of African-American and Dominican mothers and their children in New York City, which measured maternal

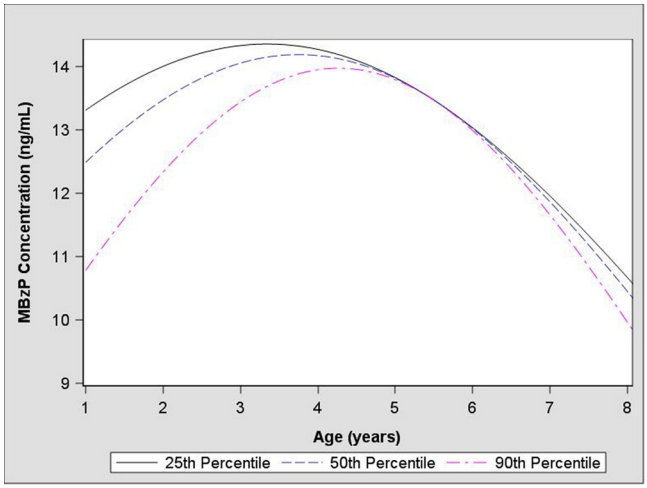

Figure 2. Adjusted trajectories of urinary MBzP concentrations in Health Outcomes and Measures of the Environment (HOME) Study children at the 25th, 50th, and 90th percentiles of body fat percent at 8 y of age. Adjusted for maternal age at delivery, race, marital status, insurance, income, education, parity, cotinine, depressive symptoms, midpregnancy body mass index (BMI), food security, prenatal fruit/vegetable and fish consumption, prenatal vitamin use, child sex, and child age at the 8-y visit.

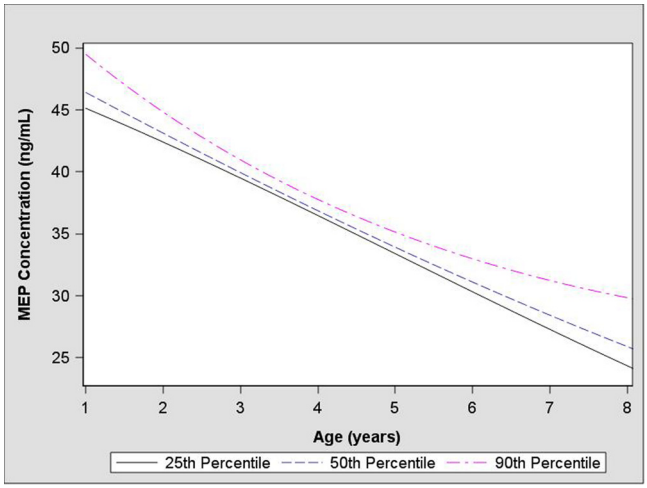

Figure 3. Adjusted trajectories of urinary MEP concentrations in Health Outcomes and Measures of the Environment (HOME) Study children at the 25th, 50th, and 90th percentiles of body fat percent at 8 y of age. Adjusted for maternal age at delivery, race, marital status, insurance, income, education, parity, cotinine, depressive symptoms, midpregnancy body mass index (BMI), food security, prenatal fruit/vegetable and fish consumption, prenatal vitamin use, child sex, and child age at the 8-y visit.

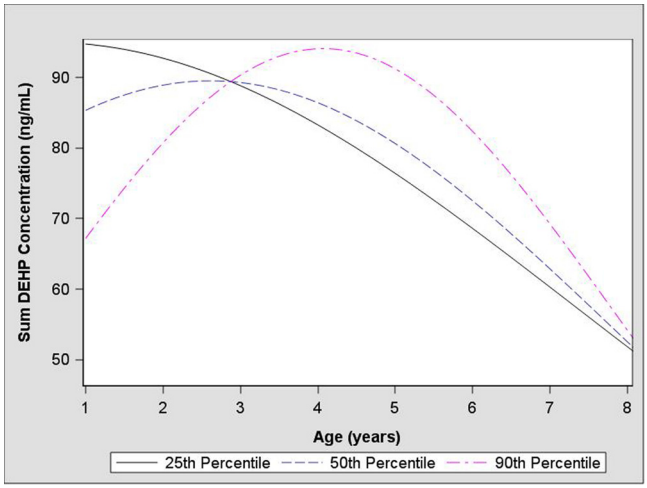

Figure 4. Adjusted trajectories of urinary ∑DEHP concentrations in Health Outcomes and Measures of the Environment (HOME) Study children at the 25th, 50th, and 90th percentiles of body fat percent at 8 y of age. Adjusted for maternal age at delivery, race, marital status, insurance, income, education, parity, cotinine, depressive symptoms, midpregnancy body mass index (BMI), food security, prenatal fruit/vegetable and fish consumption, prenatal vitamin use, child sex, and child age at the 8-y visit. Di(2-ethylhexyl) phthalate (∑DEHP) metabolites is the sum of mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP).

urinary phthalate metabolite concentrations once during the third trimester and child adiposity at ages 5 and 7 y, reported a decrease in BMI z-scores in boys with higher prenatal urine concentrations of non-DEHP metabolites and found no associations with DEHP metabolites (Maresca et al. 2016). A second study, based in Spain, measured maternal urinary phthalate metabolite concentrations during the first and third trimesters of pregnancy and child height and weight at 1, 4, and 7 y of age. They found decreasing BMI *z*-scores among boys born to mothers with higher prenatal concentrations of high-molecular-weight (HMW) phthalates, including DEHP. They reported that higher prenatal HMW phthalate metabolite concentrations were associated with increased BMI *z*-scores in girls (Valvi et al. 2015). A third study, using the same Spanish cohort described above, examined chemical mixtures and found no association between prenatal phthalate exposure and child weight at 7 y of age (Agay-Shay et al. 2015). A fourth study in New York City, which measured maternal urinary phthalate metabolite concentrations once during the third trimester and child adiposity three times between the ages 4–9 y, found a nonsignificant inverse association between prenatal ∑DEHP metabolites and body fat, but found no evidence modification by sex (Buckley et al. 2016b). Further, in a pooled cohort, which included participants from the two New York cohorts and the present study, prenatal urinary MCPP concentrations were associated with increased risk of being overweight or obese at 4–7 y of age (Buckley et al. 2016a). They also found an inverse association between prenatal ∑DEHP metabolite concentrations and BMI z-scores among girls (Buckley et al. 2016a). A sixth study, based in France, examined the association of maternal urinary phthalate metabolite concentrations measured once during pregnancy and pre- and postnatal growth of boys until 5 y of age. They reported a positive association between prenatal MEP concentrations and weight growth velocity from 2 to 5 y of age and BMI at 5 y of age (Botton et al. 2016). Finally, a study, based in Korea, analyzed the association between phthalate metabolite concentrations in infants' first urine after birth and growth during the first 3 mo of life and found a positive association between DEHP concentration and body mass increase from birth through 3 mo of age (Kim et al. 2016).

Similar to the study by Maresca et al. (2016), our study found no evidence of an association between prenatal ∑DEHP metabolites and child adiposity at age 8 y. Unlike Valvi et al. (2015) and Buckley et al. (2016a), we found no evidence that child sex modified the association between prenatal DEHP exposure and child adiposity; however, our sample size may have been too small to detect sex specific associations, as those that did find sex specific associations had sample sizes >300. While the study by Botton et al. (2016) reported a positive association between prenatal MBzP concentrations and growth velocity in the first year of life, none of the other studies found evidence of associations with MBzP. A possible explanation for the discrepant results is the considerable within-person variability of some urinary phthalate metabolite concentrations, especially MCPP and ∑DEHP. This is due to the short half-life of phthalate metabolites and episodic nature of exposures, which makes accurate exposure assessment difficult and can lead to exposure misclassification (Braun et al. 2012). Further, since some studies suggest that prenatal phthalate exposure affects growth trajectories, the different timing of adiposity measurements across studies may be a source of variability across studies (Botton et al. 2016).

Three prospective studies have examined childhood phthalate exposure and subsequent adiposity. A study of Hispanic and black children in New York City quantified urinary phthalate metabolite concentrations at approximately 7 y of age and child BMI 1 y later. They found a nonsignificant positive association of urinary MEP, MnBP, and MiBP concentrations with BMI in children that were already overweight at baseline (Teitelbaum et al. 2012). The study by Maresca et al. (2016), described above, measured child urinary phthalate metabolite concentrations at ages 3 and 5 y and adiposity at ages 5 and 7 y. They found an inverse association between urinary non-DEHP metabolite concentrations at age 5 and BMI *z*-scores at ages 5 and 7 in boys. A third study of U.S. girls, which measured urinary phthalate metabolite concentrations once between the ages of 6–8 y and anthropometry annually from 7–13 y of age, reported that higher concentrations of low-molecular-weight phthalates, including MEP, were associated with increased BMI *z*-scores and waist circumference at 7–13 y of age (Deierlein et al. 2016).

The nonsignificant positive association that we observed between urinary MEP concentrations at 5 and 8 y of age with adiposity at 8 y of age is consistent with the observations by Teitelbaum et al. (2012) and Deierlein et al. (2016). However, the associations for MBzP and ∑DEHP were discrepant across the present and prior studies. Because our results suggest that associations between DEHP and child adiposity may depend on the timing of exposure, this may be responsible for the discrepant results across studies that assessed childhood phthalate exposure at different times. The more reliable characterization of childhood urinary MEP concentrations from a single urine sample may be why the present and prior studies have observed similar patterns of results in relation to MEP concentrations, but not for other metabolites (Watkins et al. 2014). Indeed, when we examined associations between child adiposity at 8 y of age and average of urinary phthalate metabolite concentrations at 1–5 and 8 y of age, the associations between MEP (and MBzP) concentrations and adiposity became stronger and more precise than the associations between adiposity and phthalate concentrations at individual time points, which is consistent with nondifferential misclassification of phthalate exposure.

Reverse causation could explain the positive association between child MEP concentrations and adiposity, since body surface area is related to both personal care product use and

adiposity. Reverse causation could still arise when MEP is measured prospectively because MEP concentrations exhibit modest within-person correlation (Watkins et al. 2014). In addition, we show that concentrations of MEP and MBzP measured during pregnancy are weakly correlated with respective concentrations measured in the child up to 8 y later. This is likely due to shared environment, diet, and personal care product use. While we were able to mutually adjust for exposures during both pregnancy and childhood, associations between phthalates and child health outcomes could confounded in other studies lacking longitudinal exposure measures.

While it is reasonable to expect that phthalate–adiposity associations may be stronger at certain time periods, as we observed for associations between MEP or MBzP concentrations and adiposity, it is challenging to identify a biologic mechanism that would explain why phthalate–adiposity associations would be in opposite directions based on timing of exposure, as we observed with $\sum$DEHP metabolite concentrations. Given the individual variability of urinary $\sum$DEHP metabolite concentrations over time, these time-specific results may be an artifact of exposure misclassification rather than a causal association. In addition, we did not have any *a priori* biologic information regarding which time periods might be the most vulnerable to phthalate exposure. Future work in animal studies on the biology of time dependent associations can be used to inform future epidemiologic studies examining periods of vulnerability to chemical exposures.

The HOME Study has rich covariate information that allowed us to adjust for a variety of potential confounders. However, our measures of diet were crude, and it is possible that there is residual confounding from diet, as maternal/child diet may be associated with exposure to some phthalates, like DEHP, and diet quality may be associated with child adiposity (Braun 2016; Romano et al. 2014). Further, some studies have suggested a possible synergistic effect between diet and EDCs (Sargis 2015). As such, other studies with more comprehensive diet information should consider diet as a potential modifier of phthalate (or other EDC) exposure. There is also the potential for copollutant confounding due from other phthalates or other EDCs, but because the objective of this analysis was to identify periods of vulnerability, we did not employ methods to address copollutant confounding. Other studies have applied methods to address this issue (Buckley et al. 2016b), but more work in this area is needed.

As previously mentioned, phthalates are metabolized quickly, and exposure is variable. As such, a single measurement per year may not accurately characterize exposure for that year, and there is potential for exposure misclassification. However, studies have shown that concentrations of certain metabolites, particularly MEP, MnBP, MiBP, and MBzP, have fair to good correlation over time (Adibi et al. 2008; Ferguson et al. 2014; Teitelbaum et al. 2012; Watkins et al. 2014). Further, our study collected two urine samples from nearly all women during pregnancy and up to six urine samples during childhood. These multiple measures allow us to better characterize average exposure during pregnancy and try to identify unique periods of vulnerability during childhood.

There was also moderate loss to follow up in our study, as only 57% ($n = 219$) of the singleton infants had complete data and follow-up at the 8-y visit. However, sociodemographic information among the women included in our analytic sample did not differ from that of the entire sample, and prenatal phthalate concentrations were similar for children with and without 8-y data. Furthermore, our sample size may not have been large enough to detect effect modification by sex. However, we felt that it was important to consider, given the sex-specific associations observed in other studies.

O'Brien et al. (2016) suggested several methods of accounting for urine dilution with urinary creatinine concentrations. In order to maintain comparable exposure scales for our prenatal and postnatal phthalate concentrations, we chose to account for urine dilution by standardizing for creatinine as opposed to adjusting for creatinine, since different methods of accounting for creatinine could create additional errors. However, we conducted sensitivity analyses for the noteworthy phthalate–adiposity associations using two additional methods of creatinine adjustment, including creatinine as a covariate and standardizing plus covariate adjustment. The different methods produced similar results; however, associations of child adiposity with prenatal MEP, prenatal MBzP, and 8-y MEP were attenuated towards the null when we did not account for creatinine compared to any other method of accounting for urine dilution. Similarly, associations of child adiposity with 8-y MEP were attenuated when adjusting for creatinine as opposed to standardizing.

Conclusion

While we did not find strong evidence of an obesogenic effect of most of the phthalates we examined, we were able to use two statistical techniques to evaluate repeated phthalate biomarker measurements from pregnancy and childhood and determine if there are specific periods of vulnerability when exposure to phthalates may be most detrimental. The results suggest that the associations between child adiposity at 8 y of age and urinary MEP and $\sum$DEHP concentrations depended on timing of exposure. In addition, urinary MBzP concentrations during pregnancy and childhood were inversely associated with adiposity. Future studies are needed to verify these results, assess for modification by sex, and consider copollutant confounding.

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